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INFECTION OF THE MENINGES AND LUNGS BY A SPECIES OF ACTINOMYCES

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Infection of the central nervous system by branching threadlike organisms is rare. I have studied a case of primary meningeal infection with pulmonary embolic abscesses, and comparison of this case with those in the literature reveals many interesting features. I have found records of 46 instances of infection of the central nervous system by this type of organism; in 15 instances the infection was probably primary in the nervous system and in 31 the infection obviously was secondary to a chronic focus, or foci, elsewhere in the body.

Musgrave, Clegg and Polk[1] cite a series of 257 cases of infection by these organisms studied by Duvan, in which 19 showed infection of the nervous system, and a series of 109 cases studied by Ackland in which 5 showed infection of the nervous system.

ABSTRACT OF HISTORY

A white adult male, 44 years old, traveling salesman, was admitted to Barnes Hospital, Dec. 14, 1920, complaining of headache and high fever. The patient gave a history of furunculosis for the past 4 or 5 months and of having had a small pimple on the outside of his nose about 2 weeks before admission. The illness commenced Dec. 6, 1920, with a chill. Dec. 8, the patient complained of cold in the head and fever. Dec. 9 severe headache developed, with chills, and the temperature rose to 100 to 104 F. and continued until admission.

Symptoms of meningitis became more and more evident. The cerebrospinal fluid was turbid and under increased pressure. The cell count was 2,300, 88% were polymorphonuclears. Globulin and albumin were increased. The patient died Dec. 20.

Necropsy Report (F. A. McJunkin).—The body was that of a well developed and well nourished man. Both eyes protruded slightly; the conjunctivae were swollen and ecchymotic.

On the pleural surface of the left lung were about two dozen raised areas from 2 mm. to 2 cm. in diameter, which were firm and rather sharply circumscribed; the peripheries were dark red, and the centers were yellowish white, and purulent. A small amount of gas was present in a few. The pus was viscid and tenacious and brownish gray. The right lung contained about half a dozen similar nodules.

A smaller vessel at the periphery of one of the consolidated areas was occluded.

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[1] Philippine Jour. Sc., 3 Sec., B, 1908, p. 483.

On cutting the dura over the right temporal lobe a small amount of grayish pus escaped. The hypophysis was surrounded by a purulent exudate and both cavernous sinuses were completely filled with pus. In the anterior part of the middle fossa on the right side was a mass of exudate 1 cm. thick, which was adherent to the skull where the abducens and oculomotor entered. The entire base of the brain was covered with yellowish pus which extended over the right temporal lobe and to a less extent over the right frontal and occipital lobes. The involvement on the left side of the brain was less.

The vessels over the spinal cord were injected but no distinct inflammatory exudate was present.

Microscopic Examination.—The lesions in the lungs were strikingly focal; at the periphery of the areas the vessels were much distended and there was hemorrhage into the alveoli. In the centers of some areas appeared vacuoles around which were leukocytes chiefly of the neutrophilic variety, and also, a considerable number of mononuclear lekocytes some of which had ingested the neutrophils and other material. In the centers the alveolar septums had disappeared although toward the peripheries they could be recognized and contained polymorphonuclear and mononuclear cells. In the inner part of the abscess walls appeared bluish masses of bacillary forms and delicate filaments. In one section a vessel at the site of branching was completely filled with masses of organisms and granular débris; other smaller vessels in that vicinity were filled with the same material.

The entire cortex of the brain toward the base was covered with an exudate which was thickest in the sulci. Neutrophils and large mononuclear leukocytes were present in varying proportions. There were circumscribed foci consisting entirely of neutrophils and in places there were areas of large mononuclear leukocytes containing large vacuoles. In many places the distended vessels were filled with exudate, and in some of these appeared a yellowish pigment resembling disintegrated hemoglobin. Masses of organisms were present in all of these localities.

The entire pituitary body was covered with a fibrinopurulent exudate; the anterior part showed necrosis for a distance of 2 mm. The sections included the cavernous sinus which contained cellular exudate and masses of bacillary forms and what appeared to be branching organisms.

There were a few sclerotic glomeruli in the cortex near the capsule which were infiltrated with lymphocytes. Some of the tubules showed hyaline casts. In other places there was a small amount of perivascular infiltration with lymphocytes. In one small vessel was a fibrinous clot containing numerous leukocytes but no micro-organisms could be found.

In the cortex of the suprarenals were scattered suprarenal cells and foci of cells undergoing necrosis, some of which contained globules of fat. The necrotic areas were invaded by large mononuclear leukocytes.

No abnormalities were observed in the other organs.

Anatomic Diagnosis.—Septic thrombosis of cavernous sinuses; purulent meningitis; septic emboli of lungs; edema and ecchymosis of conjunctivae were diagnosed.

DESCRIPTION OF THE ACTINOMYCES

Films of pus from the lesions in the meninges and lungs stained by Gram's method showed many fairly long bacillary forms, often slightly curved with bluntly pointed, occasionally square, ends. Several bacillary forms often appeared to be in chains. Curved or comma forms and coccoid forms were not infrequent. Occasionally there was a fairly long bacillary form with spherical bodies at short intervals which were gram-positive, while the rod was slightly or not at all gram-positive. The film gave the appearance of a mixed infection. Branching was infrequent, but after long search could be found. Stained with carbolfuchsin, the picture was slightly different. The mycelia were stained as well as the disintegration products and fairly long filaments could be recognized; short bacillary and coccoid forms were also recognized. Branching appeared only slightly more frequently.

Cultures were made on blood agar in tube slants and in Petri dishes, on brown blood agar, on milk, deep gelatin, potato, deep glucose agar and on meat mediums. The meat medium was identical with that used by the Royal Medical Corps in France for growing anaerobes associated with war wounds; it was made by boiling finely ground muscle with an equal weight of tap water, made alkaline with sodium hydroxide and tubed so that about 5 c.mm. finely ground meat would be covered with 1 c.mm. of fluid in which the meat was boiled; the medium was then autoclaved.

About 30 inoculations were made in all. After 2 weeks' inoculation growth was found in one meat tube which was gradually digested as growth proceeded. The morphology of the organism in the primary culture was identical with that of the organism in the lesion. Primary subsequent inoculations from this meat tube showed no growth. Some inoculations were incubated 3 weeks in anaerobic jars and no growth took place. After inoculation of about 8 tubes each of plain broth, dextrose broth, plain broth containing hydrocele fluid, plain agar slants, glucose agar slant, plain deep agar, blood agar slant, Bordet-Gengou potato medium, milk, gelatin, potato, glycerol potato, Lubenau's egg medium, Petroff's egg medium, meat mediums and Loeffler's serum, growth was obtained on one blood agar slant. The morphology of the organism in secondary culture was identical with that observed in the primary culture. Subinoculations from this second generation grew readily on all mediums, and better aerobically than anaerobically. Young generations showed many long filaments with a few bacillary and coccoid forms. On longer incubation these same cultures showed a marked tendency toward disintegration with chain sporulation producing many bacillary and coccoid forms. No stained filaments appeared in cultures 3 months old, and all forms appeared as very short bacilli or cocci, often in chains. The formation of true spores and the presence of motility have not been observed.

The colonies were umbilicated and yellowish gray; on potato the color was frequently more yellowish. The colonies coalesced and the growth wrinkled on the surface of the medium. On an agar slant the growth penetrated the medium slightly, although it crumbled easily and particles of growth could be readily removed. On Bordet-Gengou potato medium the growth was blackish and had a metallic luster. Gelatin and Loeffler's medium were slowly liquefied. Litmus milk was slowly turned deep blue and often showed a slight coagulation which was rather soft in consistency but firm enough to remain at the bottom in a tilted tube; the lower part of the medium was gradually bleached toward a violet brown color, and evidence of digestion appeared. After a period of 3 or 4 weeks digestion was apparently complete and the fluid remaining was a muddy brownish color.

The growth over a period of three months was not alcohol-fast and not acid-alcohol-fast; however, it was not entirely decolorized by aqueous acid solution and the filaments often showed a slight brownish color when counterstained with Loeffler's methylene blue.

Intrapulmonary, intraperitoneal and subcutaneous inoculations of the pus into guinea-pigs gave negative results. Intratracheal, intravenous, intrapulmonary, intraperitoneal and subcutaneous inoculations of the pus into rabbits likewise gave negative results. Similar inoculations of the culture were negative. Intracerebral inoculations of the culture into a rabbit produced no symptoms or recognizable pathologic change.

CASES IN THE LITERATURE RESEMBLING IN SOME RESPECTS THE ONE REPORTED

Infections, probably primary in the nervous system, were described by Bollinger,[2] Musser, Pearce and Gwyn,[3] and Howard.[4] The infecting organisms were not recovered in culture and therefore only limited comparison can be made with other organisms. The morphology in each instance as shown in stained preparations was similar to the one I have described.

Naunyn[5] observed meningeal infection associated with excresences on the mitral valve; threadlike branching organisms were present in both situations. No mention of cultures was made.

Sabrazés et Rivière[6] described infection of the brain associated with lesions in the apexes of the lungs and infarct of one kidney. In stained preparations were long branching filamentous organisms some of which showed unstained areas; chains of irregular coccoid forms were occasionally seen. No filaments were found in the lesions of the lungs. All cultures were negative except for one colony which grew in deep gelatin. Subcultures failed to grow.

Almquist[7] described a case of meningeal infection unassociated with demonstrable lesions elsewhere. A large micrococcus, B. proteus, and one colony of a "streptothrix" were grown in cultures. No mention was made of finding this organism in the pus or in the sections. The source of this organism consequently is questionable. It grew luxuriantly in cultures, liquefied gelatin and produced aerial hyphae. It stained lightly with anilin dyes and showed frequent branching.

Ferré et Faguet[8] reported a case in which the infection was apparently primary in the brain. A "streptothrix" was obtained in pure culture which grew well on ordinary mediums but best on potato. It showed knoblike terminations. It was gram-positive and nopathogenic for guinea-pigs. On subdural injections in rabbits, the organisms were found in other organs but without reaction.

Eppinger[9] described an infection of the meninges associated with lesions of the lungs, pleurae, and peribronchial, mediastinal and right supraclavicular lymph nodes. A branching threadlike organism was found in the pus of the lesions and was described by Eppinger as Cladothrix asteroides. Later MacCallum[10] isolated a similar organism from a case of peritonitis and classified it as Actinomyces asteroides. This organism grew well on artificial mediums and produced a buff colored pigment. The filaments were fairly short and moderately acid-fast. Gelatin was not liquefied. It was relatively very pathogenic for laboratory animals.

From four of the cases already mentioned organisms have been cultured from the cerebral lesions. The organism isolated by Almquist, Ferré et Faguet, Eppinger and from the case here reported, were truly branching organisms which grew aerobically at room and incubator temperatures. In suppurative lesions produced by them they have appeared as interlacing masses of mycelia and not as compact colonies. They differed from one another in certain details as follows:

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[2] München. med. Wchnschr., 1887, 34, p. 789.

[3] Trans. Assn. Am. Phys., 1901, 16, p. 208.

[4] Jour. Med. Research, 1903, 9, p. 301.

[5] Mitt. a. d. Med. Klinik zu Königsberg, 1888.

[6] Presse méd., 1894, 2, p. 302.

[7] Ztschr. f. Hyg. u. Infectionskrankh., 1890, 8, p. 193.

[8] Mercredi Méd., 1895, 6. 441.

[9] Beitr. f. path. Anat. u. z. allg. Path. 1891, 9, p. 287.

[10] Centralbl. f. Bakt., O., I. 1902, 31, p. 529.

The strain described by Almquist showed aerial hyphae and liquefied gelatin.

The one described by Ferré et Faguet showed knoblike terminations and grew best on potato.

The one isolated by Eppinger showed fairly short branching filaments which were moderately acid-fast. It did not liquefy gelatin.

The one isolated from our case did not produce aerial hyphae or knoblike terminations of the filaments, and liquefied gelatin.

INFECTIONS OF THE NERVOUS SYSTEM BY BRANCHING ORGANISMS DISSIMILAR TO THE ONE NOW REPORTED

The terms actinomycosis bovis and actinomycosis hominis are used to designate chronic granulating and suppurating lesions, the pus of which contains the characteristic yellowish granules composed of dense aggregates of branching threads and their products including the characteristic refringent club-shaped bodies radially displaced at the periphery. Some variation in the organism causing typical actinomycosis has occurred.

In the case described by O. Israel,[11] the part of the process involving the vertebrae showed only leptothrix forms while the lesions elsewhere in the body showed the characteristic yellowish granules with club formation. The case described by Gangee[12] showed chronic "actinomycosis" of the trunk with secondary cerebral involvement; the pus contained interlacing masses of mycelia without club formation in any lesion. Nevertheless, it is accepted by many that true actinomycosis is caused by gram-positive organisms of the type described by Wolf and Israel in 1891. The organism described by them grew reluctantly, preferably under anaerobic conditions and at incubator temperature. Cerebral infection was preceded by actinomycosis elsewhere in the body. Infections probably occurred by contiguity of structure in some instances and in others was transmitted by the blood stream. Many of the cases of cerebral infections of this type are reviewed by Askanazy.[13]

DISCUSSION OF GRAM-POSITIVE THREADLIKE BRANCHING ORGANISMS

These organisms have been described under at least five generic names: Actinomyces, Clodothrix, Nocardia, Oospora and Streptothrix.[14] Claypole[15] considered these organisms as belonging to one genus and urged the use of streptothrix as the generic name. Wright[16] regarded Actinomyces and the organism described by Nocard as two distinct genera. He opposed the use of the names Streptothrix, Clodothrix and Oospora because they have been used previously for plant genera to which these organisms do not belong. Actinomyces was accepted by him as the generic name for the organisms causing Actinomycosis bovis and Actinomycosis hominis, and Nocardia as the generic name for the organisms similar to the one described by Nocard, which was truly branching filamentous and grew best aerobically and well at room temperature.

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[11] Berl. klin. Wchnschr., 1884, 21, S. 360.

[12] Brit. Med. Jour., 1889, 1, p. 1172.

[13] Rev. méd. de la Suisse romande, 1919, 39, p. 515.

[14] Lancet, 1910, 1, p. 551.

[15] Jour. Exper. Med., 1913, 17, p. 99.

The committee on the Society of American Bacteriologists on characterization and classification of bacterial types[17] recommended the generic name Actinomyces for the entire group with Actinomyces bovis as a type species.

Acitinomyces shows some variation in the oxygen tension requirements and in growth in gelatin. Silberschmidt[18] advanced a classification based on these cultural differences. After comparing his own strains with others obtained elsewhere he recognized the following groups:

1. Growth aerobic and at room temperature. Colonies on agar and blood serum adherent and send out numerous mycelial outgrowths into the mediums.
   (a) Liquefies gelatin; threads long; interlaced and unbroken, includes Actinomyces hominis and bovis (Boström and others) and Actinomadurae.
   (b) Does not liquefy gelatin, threads broken and often appearing in short forms, Actinomyces asteroides (Eppinger) Actinomyces caprae (Silberschmidt).
2. Colonies not adherent to mediums, gelatin not liquified, threads mostly short and many bacillary forms, "Actinomyces farcinic," and the organism obtained in Silberschmidt's Case 3.
3. Growth preferably anaerobic, colonies show no mycelial projections, and on solid medium are usually small and sharply circumscribed. No growth on gelatin or at room temperature; colonies are readily crushed and broken up. The organism does not survive as long as those of Groups 1 and 2 on artificial mediums. To this group belong the cultures from 7 of his human cases as well as those from actinomycosis of cattle.

I have found record of 8 cases of infection of the nervous system by branching threadlike organisms which were gram-negative.

Rutelli[19] reported a case of primary infection of the meninges by a "streptothrix" in a child who died 8 days after the onset of the illness. The patient had fever, vomited and developed diarrhea. The leukocyte count was

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[16] Jour. Med. Research, 1905, 13, p. 349.

[17] Jour. Bacteriol., 1920, 5, p. 191.

[18] Ztschr. f. Hyg. U. Infectionskrankh., 1901, 37, p. 345.

[19] La Pediatria, 1915, 23, p. 712.

15,000 (48% polymorphonuclear, 31% lymphocytes, 13% mononuclear and 8% other cells). In the cerebrospinal fluid were organisms in filaments which at times showed granules. This organism grew readily on Bordet-Gengou medium aerobically and showed short filaments, streptobacilli and large coccoid forms which were a little elongated. Branching was present. The organism was gram-negative, and was neither alcohol-fast nor acid-fast. Intraperitoneal injections into guinea-pigs produced a purulent peritonitis which was fatal in 3 days. The patient's blood did not contain agglutinins.

Sindoni[20] reported six cases of primary infection of the meninges in children. These occurred during an epidemic of acute cerebrospinal meningitis and all showed the symptoms of acute meningitis.

1.—A "streptothrix" occurred in pure culture from the cerebrospinal fluid.

2.—After the administration of antimeningococcus serum there was some temporary improvement in the condition. On the twelfth day after the onset a "streptothrix" was grown in pure culture from the cerebrospinal fluid.

3.—Early cultures from the cerebrospinal fluid showed the presence of the meningococcus in pure growth. Later cultures showed also the presence of a "streptothrix."

4.—Cultures from the cerebrospinal fluid showed both the meningococcus and a "streptothrix."

5.—Cultures from the cerebrospinal fluid showed the meningococcus. Some temporary improvement in the condition followed the administration of antimeningococcus serum. Later cultures gave a "streptothrix."

6.—A "streptothrix" was grown in pure culture from the cerebrospinal fluid.

Five cases were fatal. In the remaining case the outcome was not known. Sindoni considered that the meningococcus infection diminished the resistance of the patients and favored secondary infection by "streptothrix." The organisms were apperently identical with the one described by Rutelli.

Khârina-Marinucci[21] described a case of acute suppurative meningitis in a child caused by "streptothrix." The patient developed slight bronchopneumonia the cause of which was not determined. The possibility of an acute primary pulmonary infection cannot be excluded in this case. The organism was apparently identical with the ones described by Rutelli and Sindoni.

In the "Final Report of the Committee of the Society of American Bacteriologists on the Characterization and Classification of Bacterial Types," consideration is given to "Actinobacillus Brumpt," which resembles the gram-negative organisms described by Rutelli, Sindoni and Khârina-Marinucci.

SUMMARY

The gram-positive micro-organism isolated from my case grows best aerobically and well at room temperature. Under the classification given by Silberschmidt, it resembles 1a, although his description is insufficient in detail to attach it definitely to his classification. It differs from Actinomyces bovis in that it grows better under aerobic conditions and well at room temperature; from Actinomyces asteroides of Eppinger in that it liquefies gelatin; from the actinomyces of Almquist in that it does not possess arerial hyphae, and from the actinomyces of

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[20] Ibid., 1916, 24, p. 530.

[21] Ibid., 1918, 26, p. 536.

Ferré et Faguet in that it does not show knoblike terminations of the mycelia. It furthermore differs in other details.

The organisms described by Rutelli, Sindoni and Khárina-Marinucci in association with acute primary meningitis were gram-negative and distinct from the ones described by Wolf and Israel, Eppinger, Almquist Ferré et Faguet and the one from the case reported.

Six fairly distinct types of filamentous branching organisms have been isolated from infections of the nervous system. (1) Actinomyces bovis and Actinomyces hominis (doubtless identical), (2) actinomyces of Eppinger, (3) actinomyces of Almquist, (4) actinomyces of Ferré et Faguet, (5) actinomyces from the case reported, and (6) the gram-negative micro-organism described by Rutelli, Sindoni and Khárina-Marinucci.

The infection of the nervous system usually ran an acute clinical course and was fatal in all instances in which the disease was recognized (except in one case in which the outcome was not known) usually within 2 to 14 days after the onset of cerebral manifestations, although the development of the disease in several instances was apparently more insidious. The patients with actinomycosis observed by Enriquez and Sicard and Keller were benefited by decompression operations. Enriquez and Sicard's patient lived several weeks after the operation and died from acute suppurative meningitis caused by a staphylococcus. Keller evacuated the Actinomycosis abscess of the brain, and the patient was temporarily relieved. The symptoms returned in about one year and a second operation was performed, the patient dying soon after.

The lesions in the brain usually were represented by single or multiple abscess formation associated with more or less purulent meningitis, and in several instances by purulent meningitis without abscess formation. There is a record of thrombosis of the larger venous channels in one case described by Ponfick,[22] in one by Moosbrugger,[23] and in two cases by Askanazy,[13] to which our case may be added.

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[22] Die Actinomykose des Menschen, 1882.

[23] Beitr. z. klin. Chir., 1886, 2, p. 339.